ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

A REVIEW ARTICLE ON POLYCYSTIC OVARIAN SYNDROME

Mogili Komali*, Siddhartha Lolla , Kallam Veena Maheshwar Reddy,
Outkur Bhagyasri, Maddati Prasanna, Borgau Sai Vaishali, Nagula Ranjith

Department of Pharmacology, Pulla Reddy Institute of Pharmacy, Dundigal, Sanga Reddy, Telagana-502313, India

*Corresponding author E-mail: outkurbhagyasri@gmail.com

ARTICLE INFO

Key words:

Polycystic ovarian syndrome (PCOS) GLP-1 agonists, DPP4 inhibitors, and SGLT2 inhibitors.

Access this article online
Website:
https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age globally. Diagnosed based on the presence of at least two criteria among polycystic ovaries, hyperandrogenism, and chronic anovulation, PCOS poses diagnostic challenges due to overlapping symptoms with other disorders. Its etiology is multifactorial, involving genetic predisposition and environmental triggers such as obesity and insulin resistance. The condition is underdiagnosed, leading to delayed intervention and associated comorbidities, including metabolic syndrome, infertility, and cardiovascular risks. Understanding its pathophysiology reveals that hyperandrogenism and dysregulation of ovarian steroidogenesis play central roles. Accurate diagnosis requires careful exclusion of other conditions and consideration of specific adolescent presentations. Imaging advances have refined the detection of polycystic ovarian morphology. Management strategies prioritize lifestyle modifications, hormonal therapy, and emerging pharmacological options like GLP-1 agonists, DPP4 inhibitors, and SGLT2 inhibitors. Accurate diagnosis requires careful exclusion of other conditions and consideration of specific adolescent presentations. Imaging advances have refined the detection of polycystic ovarian morphology. Management strategies prioritize lifestyle modifications, hormonal therapy, and emerging pharmacological options like GLP-1 agonists, DPP4 inhibitors, and SGLT2 inhibitors. Research into treatments such as myoinositol supplements and PPARγ agonists continues to evolve. Early diagnosis and comprehensive management are crucial to improve the quality of life in affected individuals

INTRODUCTION:

PCOSor polycystic ovarian syndrome, is the most prevalent endocrine disorder affecting reproductive females globally. It was first described in 1935 by Stein and Leventhal. The diagnostic criteria used determine the prevalence, which varies from 5% to 15%. According to specialist society recommendations, the diagnosis of PCOS must be made based on the presence of at least two of the three criteria listed below: polycystic ovaries, clinical or biological hyperandrogenism, and chronic anovulation. Conditions that resemble the clinical manifestations of PCOS must be ruled out because it is an exclusionary diagnosis. These include hyperprolactinemia, non-classical congenital adrenal hyperplasia, and thyroid disorders. More thorough workup may be required for selected patients if clinical signs point to alternative causes. PCOS is underdiagnosed despite its high incidence, and it sometimes requires multiple visits or various doctors to be diagnosed, usually over

a period of more than a year. The patient finds the process to be quite frustrating. Comorbidities might worsen as a result of delayed diagnosis, making lifestyle interventions—which are essential for improving PCOS symptoms and quality of life—more challenging to carry out. Obstructive sleep apnea (OSA), endometrial cancer, obesity, metabolic syndrome, infertility, impaired glucose tolerance, type 2 diabetes mellitus, cardiovascular risk, depression, and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) are among the many morbidities linked to PCOS.Each of these diseases has a separate screening suggestion, but if PCOS patients exhibit any symptoms, the clinician needs to have a low threshold for workup[1][2][3].

ETIOLOGY:

Multifactorial PCOS is a disease. Numerous vulnerable genes have been shown to play a role in the disease's pathogenesis. These genes participate in different stages of androgenic pathways and steroidogenesis. Heritability has been estimated at 70% by twin studies. Additionally, the environment has a crucial role in how these genes are expressed as well as how the illness develops and advances.[4], [5], [6] Two widely accepted theories suggest that people with a genetic predisposition who are exposed to specific environmental circumstances display the characteristics of PCOS. The two environmental factors that are most prevalent are insulin resistance and obesity. Exposure to prenatal androgen is another theory.[7]

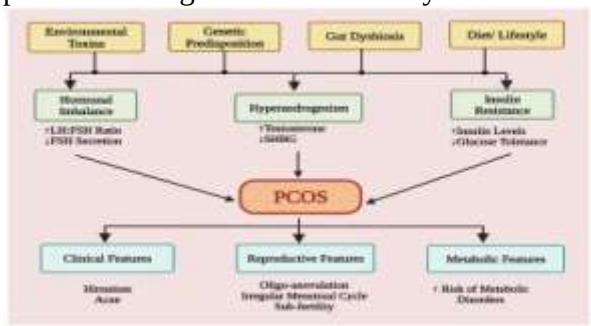

Figure 1:Etiology of PCOs

EPIDEMIOLOGY:

As previously said, PCOS is the most prevalent endocrine disorder in women of reproductive age globally, impacting 5% to 15% of females based on diagnostic standards. Compared to the National Institute of Health 1990 Criteria, the Rotterdam criteria include a wider range of prevalence. An estimated 5 million females in the United States who are of reproductive age suffer from PCOS, according to the NIH 2012 workshop report. Not considering the expense of severe comorbidities linked to PCOS, the annual cost of diagnosing and treating PCOS to the healthcare system is about $4 billion. Infertility, metabolic syndrome, obesity, impaired glucose tolerance, type 2 diabetes mellitus, cardiovascular risk, depression, OSA, endometrial cancer, and NAFLD/NASH are among the disorders that have been linked to PCOS. Premature adrenarche, congenital virilizing diseases, prepubertal obesity, above-average or low birth weight for gestational age, first-degree relatives with PCOS, and the use of valproic acid as an antiepileptic medication have all been linked to higher prevalence. Additionally, research has indicated that Mexican Americans are more likely to have it than non-Hispanic whites and African Americans.[8][9].

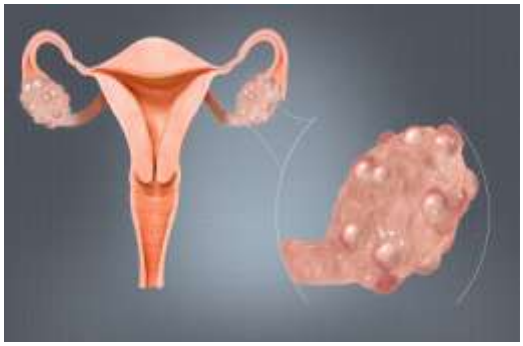

Figure 2: Epidemiology of PCOs

PATHOPHYSIOLOGY:

PCOS is an oligo-anovulation hyperandrogenic state that cannot be explained by any other disorder. A diagnosis of exclusion is what it is. The majority of hyperandrogenic presentations, however, are caused by it. Fibroovarianhyperandrogenism (FOH) is the cause of almost all PCOS causes. Two-thirds of PCOS cases present with typical functional ovarian hyperandrogenism, which is defined by an excess of 17-hydroxyprogesterone (17-OHP) in response to gonadotropin stimulation and dysregulation of androgen production. The remaining PCOS has an abnormal 17-OHP FOH response; nonetheless, after adrenal

androgen synthesis is suppressed, testosterone rise is observed. Isolated functional adrenal hyperandrogenism is associated with PCOS in approximately 3% of patients. The remaining cases of PCOS are minor. The majority of these individuals are obese, which clinicians believe explains their atypical PCOS; they show no signs of steroid secretory abnormalities. Currently, there is little clinical value in specific testing for the FOH subgroup.[10]Hyperandrogenism, oligoanovulation, and polycystic ovarian morphology are the main symptoms of functional ovarian hyperandrogenism (PCOS). A mix of environmental and genetic variables contribute to functional ovarian hyperandrogenism. An inherent imbalance among intraovarian regulatory systems and insulin excess, which is known to sensitize the ovary to luteinizing hormone (LH) by interfering with the process of homologous desensitization to LH in the normal ovulation cycle, are the causes of this dysregulation. The majority of steroidogenic enzymes and proteins involved in androgen production are overexpressed in PCOS theca cells, indicating a significant anomaly in the amount and activity of steroidogenic enzymes, including the well-known P450c17. Excess androgen and insulin are the main causes of early luteinization in granulosa cells. Primordial follicles are initially recruited into the growth pool more effectively by androgen excess. It hinders the dominant follicle selection and starts premature luteinization at the same time. This leads to the gross anatomical changes that make up polycystic ovarian morphology (PCOM) and the characteristic histopathologic modifications of PCOS. PCOS is not caused by increased LH, rather it is perpetuated by it. Although LH excess is widespread and essential for the production of sex hormones and the expression of gonadal steroidogenic enzymes, it is less likely to be the main source of ovarian androgen excess due to the desensitization of theca cells caused by LH. An aberrant degree of insulin-resistant hyperinsulinism, which acts on theca cells, luteinizes granulosa cells, increases steroidogenesis prematurely, and promotes fat formation, is present in approximately one-half of patients with functional ovarian hyperandrogenism. Excess LH is triggered by hyperandrogenism and affects the luteinized granulosa and theca to maintain the cycle. The pulsatile gonadotropin-releasing hormone release is altered by ovarian hormonal dysregulation, which may result in a relative increase in the production and secretion of LH as opposed to follicle-stimulating hormone (FSH). While the relative decrease of FSH hinders sufficient activation of aromatase activity within the granulosa cells, hence reducing androgen conversion to the powerful estrogen estradiol, LH boosts ovarian androgen synthesis. This turns into a noncyclic, self-replicating hormonal rhythm. In the peripheral, elevated serum androgens are transformed into estrogens, primarily estrone. Obese PCOS individuals produce more estrogen because conversion mostly takes place in the stromal cells of adipose tissue. In contrast to the typical feedback variations seen in the presence of a developing follicle and rapidly fluctuating estradiol levels, this conversion causes continuous feedback at the hypothalamus and pituitary gland. Endometrial hyperplasia can result from unopposed estrogen stimulation of the endometrium.[11][12] [13] To diagnose PCOS, a thorough medical history and physical examination are essential. Menstrual history and hyperandrogenism characteristics are among the two out of three diagnostic criteria that depend on the history and physical examination. Furthermore, PCOS is an exclusionary diagnosis, so it is important to determine how other illnesses manifest clinically.The majority of people who match two of the three criteria—chronic anovulation, clinical or biological hyperandrogenism, and polycystic ovarian morphology in the absence of any other pathology—are diagnosed with PCOS, according to the majority of society's recommendations. The Rotterdam Criteria include these clinical characteristics. Additionally, oligo or anovulation and clinical or biochemical hyperandrogenism are required per the National Institutes of Health standards. Hyperandrogenism must meet one of the two remaining criteria set forth by the American Excess PCOS Society. It is important to rule out conditions that resemble

the clinical signs of PCOS. These include non-classic congenital adrenal hyperplasia with 21-hydroxylase deficiency, thyroid disease, and hyperprolactinemia. Serum 17-hydroxyprogesterone (17-OHP) should be measured for these conditions, which may necessitate additional testing using the adrenocorticotropin stimulation test.[14][15][16]It is particularly difficult to diagnose PCOS in adolescents because of their developmental problems. Many of the characteristics of PCOS, such as acne, irregular menstruation, and hyperinsulinemia, are typical of normal puberty. The hypothalamic-pituitary-ovarian axis is immature during the first two to three years after menarche, which results in irregular menstruation and anovulatory cycles. After this time, persistent oligomenorrhea indicates a higher likelihood of underlying ovarian or adrenal disease as well as continued irregular menstruation.Chronic anovulation is suggested by a cycle length greater than 35 days, however ovulatory dysfunction must be evaluated if the cycle length is between 32 and 35–36 days. For adults, the threshold for oligomenorrhea is 35 days, and for teenagers, it is 40 days. Progesterone levels in the mid-luteal phase (20–21 days) can be used to evaluate a patient whose cycles are less than 35 days. Ovulatory failure can lead to endometrial cancer, endometrial hyperplasia, and infertility.

Figure 3: PCOs

POLYSTISTIC OVARIAN MORPHOLOGY :

Transvaginal ultrasonography provides a more accurate assessment of ovarian morphology. PCOM can be diagnosed in patients with at least 25 tiny follicles (2 mm to 9 mm) over the entire ovary thanks to new ultrasound equipment. The typical size threshold for ovarian size is still 10 ml. According to the 2004 Rotterdam criteria, PCOM is indicated by at least 12 ovarian follicles that measure between 2 and 9 mm or by an ovary that is larger than 10 ml. With the advancement of ultrasound technology, PCOS diagnosis can be improved. After reviewing recent evidence, the Androgen Excess and PCOS Society released amended recommendations for diagnosing PCOM, raising the follicle count to 25. The size of the ovaries has not changed. Body weight and fat distribution do not differ between women with PCOS and those in good health. The first dose of an oral contraceptive is 20 mcg of ethinyloestradiol mixed with progestin that has neutral effects like norethindrone acetate or antiandrogenic qualities like desogestrel and drospirenone. It has been demonstrated that progestin with antiandrogenic qualities increases the incidence of venous thromboembolism (VTE). Ethinyloestradiol can be increased to 30 to 35 mcg if the initial dose is insufficient to fully treat hyperandrogenic symptoms.

TREATMENT:

LIFESTYLE MODIFICATION:

The most effective first-line treatments for weight loss and IGT in overweight and obese PCOS women and adolescents are calorie-restrictive diets and exercise. Numerous studies have demonstrated that hirsutism can enhance and control ovulation and the menstrual cycle. Although low-carb diets have been employed in the hopes that they may have a greater impact on hyperinsulinism, research has not found any differences in the results of these diets.[3][17] [18]

HORMONAL CONTRACEPTIVES:

Hormonal contraceptives, such as vaginal rings, patches, or oral contraceptives, are the first line of treatment for hirsutism, acne, and irregular menstruation. No option is preferred over another by the Endocrine Society. The progestin component raises sex hormone-binding globulin and indirectly lowers ovarian androgen synthesis by lowering LH levels. Furthermore, it has been demonstrated that certain progestins directly limit the activity of 5 alpha-reductase, preventing the conversion of free testosterone into its more potent form, 5 alpha-dihydrotestosterone, hence having

antiandrogenic effects. They are therefore quite successful in managing the menstrual cycle and hyperandrogenism symptoms.

Every patient should be screened for hormonal contraceptive contraindications. Absolute contraindications include uncontrolled diabetes with severe peripheral vascular disease, uncontrolled hypertension more than 160/100, and smoking more than 15 cigarettes per day by women aged 35 or older. When there are several comorbidities, the US Medical Eligibility Criteria for Contraceptive Use are helpful. Hormonal contraceptives are not contraindicated for patients with diabetes who do not have vascular problems. Higher estrogen activity raises HDL cholesterol and lowers LDL cholesterol in relation to the metabolic effects of hormonal contraceptives.

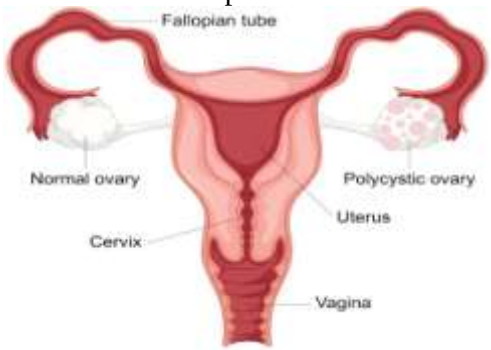

Figure 4: Hormonal contraceptives

ADDITIONAL TREATMENT IN PCOS :

- **GLP-1 agonists**

GLP-1 agonists attach to the GLP-1 receptor and cause the pancreatic islets to release insulin in response to glucose. Because they are resistant to being broken down by the enzyme dipeptidyl peptidase 4 (DPP-4), they have a longer half-life than our bodies' GLP-1. Research indicates that obese individuals with PCOS had considerably lower levels of GLP-1 secretion than lean women.[24] In obese women with PCOS, GLP-1 agonist treatment was linked to better ovulation rates and lower BMI and testosterone levels.[25] There is growing evidence that GLP-1 agonists are more effective than metformin at promoting weight loss and improving insulin sensitivity.[26] The expensive cost of the drugs and insurance companies' lack of coverage may hinder the widespread use of GLP-1 agonists in PCOS treatment.

DPP4 inhibitors- DPP4 inhibitors increase glucose-dependent insulin release by reducing incretin breakdown. They are regarded as being weight neutral in individuals with type 2 diabetes. According to recent research, DPP4 inhibitors can help obese women with PCOS lose weight and lower their blood sugar levels. Additionally, they stopped women who were switching from GLP-1 agonists from gaining weight. Research indicates that DPP4 inhibitors' impact on PCOS-afflicted women's weight is based on an increase in growth hormone, which is decreased in PCOS patients. Consequently, visceral fat mass is reduced. It is still regarded as experimental and has little data.[27].

Figure 5: PCOs

- **SGLT-2 inhibitors:**

In patients with type 2 diabetes, SGLT2 inhibitors improve weight loss and cardiovascular risk by increasing urine glucose secretion. When SGLT2 inhibitors are used instead of metformin, there is encouraging evidence of weight loss and a decrease in body fat in obese patients. Nevertheless, it had a comparable impact on metabolic and hormonal markers. To use this drug in clinical practice, more information is required.[28]

Peroxisome proliferator-activated receptor gamma (PPARg) agonist: Treatment with PPARg agonists in PCOS improved metabolic and hormonal outcomes, but weight was negatively impacted. When compared to metformin, it may be better for patients with NAFLD.[29]

Myoinositol: An over-the-counter dietary supplement called myoinositol improves insulin sensitivity. Insulin sensitivity in PCOS-afflicted women was enhanced as compared to a placebo, although BMI was not much impacted. Due to its less gastrointestinal side effects, it has mostly been used as a reproductive medication for

PCOS or when metformin is not tolerated. However, data on its effectiveness is limited.[30]

REFERENCES:

1. Ding DC, Chen W, Wang JH, Lin SZ. Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: A population-based cohort study in Taiwan. Medicine (Baltimore). 2018 Sep;97(39):e12608. [PMC free article] [PubMed]
2. Zhang C, Ma J, Wang W, Sun Y, Sun K. Lysyl oxidase blockade ameliorates anovulation in polycystic ovary syndrome. Hum Reprod. 2018 Nov 01;33(11):2096-2106. [PubMed]
3. Norman RJ, Teede HJ. A new evidence-based guideline for assessment and management of polycystic ovary syndrome. Med J Aust. 2018 Sep 01;209(7):299-300. [PubMed]
4. Goyal A, Ganie MA. Idiopathic Hyperprolactinemia Presenting as Polycystic Ovary Syndrome in Identical Twin Sisters: A Case Report and Literature Review. Cureus. 2018 Jul 19;10(7):e3004. [PMC free article] [PubMed]
5. Albu D, Albu A. The relationship between anti-Müllerian hormone serum level and body mass index in a large cohort of infertile patients. Endocrine. 2019 Jan;63(1):157-163. [PubMed]
6. Spinedi E, Cardinali DP. The Polycystic Ovary Syndrome and the Metabolic Syndrome: A Possible Chronobiotic-Cytoprotective Adjuvant Therapy. Int J Endocrinol. 2018;2018:1349868. [PMC free article] [PubMed]
7. Puttabyatappa M, Padmanabhan V. Ovarian and Extra-Ovarian Mediators in the Development of Polycystic Ovary Syndrome. J MolEndocrinol. 2018 Oct 16;61(4):R161-R184. [PMC free article] [PubMed
8. Hallajzadeh J, Khoramdad M, Karamzad N, Almasi-Hashiani A, Janati A, Ayubi E, Pakzad R, Sullman MJM, Safiri S. Metabolic syndrome and its components among women with polycystic ovary syndrome: a systematic review and meta-analysis. J CardiovascThorac Res. 2018;10(2):56-69. [PMC free article] [PubMed]
9. Maya ET, Guure CB, Adanu RMK, Sarfo B, Ntumy M, Bonney EY, Lizneva D, Walker W, Azziz R. Why we need epidemiologic studies of polycystic ovary syndrome in Africa. Int J Gynaecol Obstet. 2018 Nov;143(2):251-254. [PubMed]
10. Carvalho LML, Dos Reis FM, Candido AL, Nunes FFC, Ferreira CN, Gomes KB. Polycystic Ovary Syndrome as a systemic disease with multiple molecular pathways: a narrative review. EndocrRegul. 2018 Oct 01;52(4):208-221. [PubMed]
11. Marciniak A, Lejman-Larysz K, Nawrocka-Rutkowska J, Brodowska A, Songin D. [Polycystic ovary syndrome - current state of knowledge]. Pol MerkurLekarski. 2018 Jun 27;44(264):296-301. [PubMed]
12. Sala Elpidio LN, de Alencar JB, Tsuneto PY, Alves HV, Trento Toretta M, It Taura SK, LaguilaVisentainer JE, Sell AM. Killer-cell immunoglobulin-like receptors associated with polycystic ovary syndrome. J ReprodImmunol. 2018 Nov;130:1-6. [PubMed]
13. Shorakae S, Ranasinha S, Abell S, Lambert G, Lambert E, de Courten B, Teede H. Inter-related effects of insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflammation in PCOS. ClinEndocrinol (Oxf). 2018 Nov;89(5):628-633. [PubMed]
14. Xie J, Burstein F, Garad R, Teede HJ, Boyle JA. Personalized Mobile Tool AskPCOS Delivering Evidence-Based Quality Information about

Polycystic Ovary Syndrome. SeminReprod Med. 2018 Jan;36(1):66-72. [PubMed]
15. Boyle JA, Xu R, Gilbert E, Kuczynska-Burggraf M, Tan B, Teede H, Vincent A, Gibson-Helm M. Ask PCOS: Identifying Need to Inform Evidence-Based App Development for Polycystic Ovary Syndrome. SeminReprod Med. 2018 Jan;36(1):59-65. [PubMed]
16. Misso ML, Tassone EC, Costello MF, Dokras A, Laven J, Moran LJ, Teede HJ., International PCOS Network. Large-Scale Evidence-Based Guideline Development Engaging the International PCOS Community. SeminReprod Med. 2018 Jan;36(1):28-34. [PubMed]
17. Tay CT, Moran LJ, Wijeyaratne CN, Redman LM, Norman RJ, Teede HJ, Joham AE. Integrated Model of Care for Polycystic Ovary Syndrome. SeminReprod Med. 2018 Jan;36(1):86-94. [PubMed]
18. Htet T, Cassar S, Boyle JA, Kuczynska-Burggraf M, Gibson-Helm M, Chiu WL, Stepto NK, Moran LJ. Informing Translation: The Accuracy of Information on Websites for Lifestyle Management of Polycystic Ovary Syndrome. SeminReprod Med. 2018 Jan;36(1):80-85. [PubMed]
19. Glintborg D, Altinok ML, Mumm H, Hermann AP, Ravn P, Andersen M. Body composition is improved during 12 months' treatment with metformin alone or combined with oral contraceptives compared with treatment with oral contraceptives in polycystic ovary syndrome. J ClinEndocrinolMetab. 2014 Jul;99(7):2584-91. [PubMed]
20. Ganie MA, Khurana ML, Nisar S, Shah PA, Shah ZA, Kulshrestha B, Gupta N, Zargar MA, Wani TA, Mudasir S, Mir FA, Taing S. Improved efficacy of low-dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six-month, open-label randomized study. J ClinEndocrinolMetab. 2013 Sep;98(9):3599-607. [PubMed]
21. Glintborg D, Andersen M. Medical comorbidity in polycystic ovary syndrome with special focus on cardiometabolic, autoimmune, hepatic and cancer diseases: an updated review. CurrOpinObstet Gynecol. 2017 Dec;29(6):390-396. [PubMed]
22. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ., International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. ClinEndocrinol (Oxf). 2018 Sep;89(3):251
23. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ., International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. FertilSteril. 2018 Aug;110(3):364-379. [PMC free article] [PubMed]
24. Glintborg D, Mumm H, Holst JJ, Andersen M. Effect of oral contraceptives and/or metformin on GLP-1 secretion and reactive hypoglycaemia in polycystic ovary syndrome. Endocr Connect. 2017 May;6(4):267-277. [PMC free article] [PubMed]
25. Niafar M, Pourafkari L, Porhomayon J, Nader N. A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries. Arch Gynecol Obstet. 2016 Mar;293(3):509-15. [PubMed]
26. Han Y, Li Y, He B. GLP-1 receptor agonists versus metformin in PCOS: a systematic review and meta-analysis. Reprod Biomed Online. 2019 Aug;39(2):332-342.
27. Devin JK, Nian H, Celedonio JE, Wright P, Brown NJ. Sitagliptin

Decreases Visceral Fat and Blood Glucose in Women With Polycystic Ovarian Syndrome. J ClinEndocrinolMetab. 2020 Jan 01;105(1):136-51. [PMC free article] [PubMed]

28. Javed Z, Papageorgiou M, Deshmukh H, Rigby AS, Qamar U, Abbas J, Khan AY, Kilpatrick ES, Atkin SL, Sathyapalan T. Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: A randomized controlled study. ClinEndocrinol (Oxf). 2019 Jun;90(6):805-813. [PubMed]
29. Tay CT, Joham AE, Hiam DS, Gadalla MA, Pundir J, Thangaratinam S, Teede HJ, Moran LJ. Pharmacological and surgical treatment of nonreproductive outcomes in polycystic ovary syndrome: An overview of systematic reviews. ClinEndocrinol (Oxf). 2018 Nov;89(5):535-553. [PubMed]
30. Zeng L, Yang K. Effectiveness of myoinositol for polycystic ovary syndrome: a systematic review and meta-analysis. Endocrine. 2018 Jan;59(1):30-38. [PubMed]